AUGUST 1961

Disease-a-Month

Coma

E. CHARLES KUNKLE

YEAR BOOK MEDICAL PUBLISHERS • INC.
CHICAGO

DM

Disease-a-Month

MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

RECENT AND FORTHCOMING ISSUES

S. Magnusson and *W. C. Moloney*—MULTIPLE MYELOMA

Martin M. Cummings and *Max Michael, Jr.*—SARCOIDOSIS

H. B. Mulholland, John A. Owen, Jr. and *J. Brookins Taylor*—COMPLICATIONS OF DIABETES MELLITUS

Robert P. McCombs—PERIARTERITIS NODOSA AND RELATED DISORDERS OF BLOOD VESSELS

Maxwell Finland—CHEMOPROPHYLAXIS OF INFECTIOUS DISEASES (3 PARTS)

Stewart Wolf—THE ACUTE ANXIETY STATE

Harvey Rothberg and *Harold Jeghers*—EXTERNAL MANIFESTATIONS OF INTERNAL DISEASE

Theodore B. Schwartz and *Robert N. Hedges, Jr.*—HYPERCALCEMIA AND HYPOCALCEMIA

Russell N. DeJong—PARKINSONISM

Wallace N. Jensen—THE HEMOGLOBINOPATHIES

PRINTED IN U.S.A.

Coma

E. CHARLES KUNKLE

TABLE OF CONTENTS

E. Charles Kunkle

is Chief of the Division of Neurology and Professor of Neurology at Duke University Medical Center. He received his M.D. degree from Cornell University Medical College and served his internship and residency at New York Hospital. Dr. Kunkle is a member of the American Neurological Association and a Fellow of the American College of Physicians. His principal research interests have been in headache and pain mechanisms and disorders in cranial circulation.

MAN MUST BE AWAKE much of the time to survive. He can neither eat nor drink nor even reproduce, unless he is reasonably aware; hence his jeopardy whenever he enters a coma. To compound the danger, he then can give no history, is examined with difficulty and is vulnerable to complicating illnesses.

The significance of coma has long been recognized in history and legend from Socrates to Snow White. In fact or fable, coma may be brief or prolonged, benign or lethal, abrupt or insidiously slow in onset, and obvious or obscure in origin. A review of its nature must extend from physiologic experiment to clinical observation. From these data can be outlined current views of the mechanisms of coma, general principles in the evaluation and treatment of the comatose patient and details of management of certain major varieties of coma.

MECHANISMS OF CONSCIOUSNESS AND ITS LOSS

In both a psychologic and a clinical sense coma can be viewed simply as complete unconsciousness. Yet its opposite, the con-

ventional, essential and desirable condition of man, is itself not easily defined. Consciousness is not an all-or-none affair. It represents the complex interaction of many cortical and deep-lying regions of the brain, and its physiologic basis cannot be described in one sentence or one paragraph (1).

The transition from consciousness to unconsciousness is one of many gradations. The separate levels are analyzed best in terms of what the individual can and cannot do in each. The definitions are thus mainly operational.

Full consciousness, in essence, is awareness of environment and of self; the individual is alert to signals from without and within and is able to interpret such information, to make proper perceptual discriminations and to react when action is called for. In the human animal, at least, consciousness implies awareness of being aware and permits perception, thought and activity of widely differing degrees of complexity. The conscious man can do more than digest food, pump blood and form urine. He can brush away a buzzing fly, pay a bill (or persuade his wife to do so) and plan a weekend trip.

The opposite pole, unconsciousness, including its deepest level, coma, is defined more readily; it is easier to describe the deficiencies of a machine than its complete potential. In coma the individual is unaware and exists largely in terms of basal automatic bodily functions. He can be aroused at best only slightly, even with protracted vigorous stimulation, and the arousal may be manifest only in a small restless movement or a faint acceleration of the cardiac or respiratory rate.

The progression from full consciousness to coma may occur abruptly or gradually. When slow, the progressive impairment of various mental faculties can be seen by close observation as the patient becomes drowsy, then stuporous and then comatose. The usual features of these successive steps are summarized in Table 1. In many instances, predictable changes in the electrical activity of the brain develop with each stage. The principal trend is a slowing of the basic rhythms as detected at the cortex, passing from the normal 8–12/sec. alpha range of the resting but wakeful brain, through the 5–7/sec. theta range, down to the 1–4/sec. delta range of coma. These approximate correlations are indicated in the table.

TABLE 1.—Levels of Consciousness: EEG and Behavioral Correlates*

Level	Electroencephalogram	State of Awareness	Behavioral Efficiency
Alert attentiveness	Partially synchronized; mainly fast waves of low amplitude	Selective attention, but may vary or shift	Good: efficient, selective, quick reactions, organized for serial responses
Relaxed wakefulness	Synchronized; optimal alpha rhythm	Attention wanders; favors free association	Good: routine reactions and creative thought
Drowsiness	Reduced alpha and occasional slow waves of low amplitude	Borderline, partial awareness; imagery and reverie	Poor: uncoordinated, sporadic, lacking sequential timing
Light sleep	Spindle bursts and larger slow waves; loss of alpha	Markedly reduced consciousness; dream state	Absent
Deep sleep *(stupor)*	Large and very slow waves (synchrony but on slow time bases); random irregular pattern	Unconsciousness; partial arousal on vigorous stimulation; amnesia for stimuli or dreams	Absent
Coma	Isoelectric to irregular large slow waves	Complete loss of consciousness; little or no response to stimulation; amnesia	Absent
Death	Isoelectric: gradual disappearance of all electrical activity	Complete loss of all responses	Absent

*Modified from scheme of Lindsley (2).

The dissolution of brain function is not always as straightforward as the table might imply. Dissociations may occur in the loss of separate brain faculties as impairment of consciousness proceeds. A familiar example is the preservation of speech and organized movement in some individuals during sleep, as observed in the sleep-talker and the sleep-walker. Elaborate dreams are equally striking indicators that higher brain functions may still operate, although in altered fashion, during sleep. Even in stupor a patient may automatically but efficiently yawn, rub his nose, or open his eyes and vaguely scan his environment.

Sleep

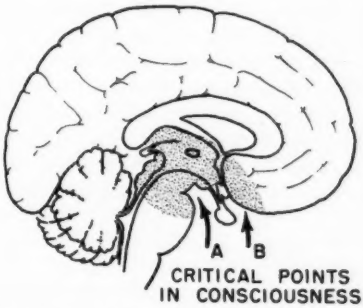
Normal sleep, it must be stressed, occupies a special place in the analysis of unconsciousness and its variations. Sleep is a state in which full awareness is temporarily suspended to good purpose. It occurs periodically under predictable circumstances—at the close of a period of activity, when one isolates oneself from distractions by lying in comfort in a quiet and darkened room. The process is aided by conditioning, through repeated experience, starting in infancy, of the same sequence of preparations for bed. In most of us arousal from sleep is readily achieved when the usual quota of rest has been filled or by the intrusion of a sound, touch or other stimulus.

Abnormal sleep is often unduly deep or prolonged and occurs under inappropriate circumstances. It is then termed stupor. It may, in the diseased brain, represent a stage en route to coma. Another variety occurs in patients with narcolepsy, who show a curious susceptibility to falling asleep on such slight provocation as mere inactivity at any point in a day's program.

The Activating System

The cerebral cortex has long been recognized as essential to the highest level activities of the central nervous system, including memory, perceptual discrimination, learning and consciousness. Neurophysiologic experiments of the past two decades have focused new attention, however, on certain deep-lying structures of equally vital importance to the maintenance of consciousness. These lie within the brain stem, particularly from the pons upward, in the network known as the reticular substance or forma-

tion, enveloping many nuclear groups and fiber tracts of familiar name and function. The connections of the reticular formation with local and outlying zones are largely uncharted, but it is now clear that into it are channeled ascending impulses from the multiple sensory receptors of the body. These same messages travel also by more direct and classical routes to their specific destinations in the lateral masses of the thalamus and then on to the cerebral cortex. Through the collateral and nonspecific sensory connections in the reticular formation, relayed diffusely to the cortex, consciousness is sustained. This is the concept of the ARAS, or "ascending reticular activating system" (3).



Regions of the upper brain stem and diencephalon *(marked by stippling)* vital to the maintenance of consciousness. These include the posterior (*A*) and anterior (*B*) "critical points" described by Jefferson (4), the principal boundaries of the ascending reticular activating system.

Another and perhaps more flexible alerting service is provided by collateral connections from sensory receptors to medial areas of the thalamus, lying adjacent to the third ventricle and representing the "diffuse thalamic projection system." These alerting systems, charted in the accompanying figure, are at the core of the brain — the midbrain, hypothalamus, paraventricular portions of the thalamus and the septal region adjacent to the anterior commissure—and upon them the cortex relies for its adequate performance as an organ of consciousness. If sensory input to these systems is sufficiently reduced, as when we go to bed, cortical excitability wanes and consciousness is

replaced by sleep. If these structures are so damaged by disease that the upstream activating impulses are blocked, particularly at the limits designated by Jefferson (4) as posterior and anterior critical points (*A* and *B* of the figure), consciousness is likely to be impaired, even to the point of coma.

The interest currently invested by psychologists and physiologists in the reticular activating system should not be allowed to detract from the importance to consciousness of the cerebral cortex. Clinical experience supports this view, for as Walker (5) has stated: "Although the cerebral cortex may be only a suburban area, a . . . disturbance of it is devastating to the nature of the organism even if the reticular formation be intact." The cortex itself influences the reticular substance and aids in maintaining its excitability. Perhaps in part through this relationship arise the impairments of consciousness which sometimes result from lesions restricted to the cortex. A warning is warranted also with reference to the uncertainties still surrounding the morphology of the activating system. Its intricate interconnections are almost certainly multisynaptic and its precise limits are conjectural. It is as yet much more a physiologic concept than an anatomic entity.*

Coma as a Form of Brain Failure

Coma, regardless of mechanism, is a sign of brain failure. Other vital organs, such as the heart or liver, fail in relatively limited ways. The much more elaborate brain can prove incompetent in numerous functions. When the fault is confined to one anatomic area, the impairment may be circumscribed, as in the homonymous hemianopsia of an occipital lobe infarction. When the fault is more general within the brain, the insufficiency is likely to be largely in the highest cerebral activities, those of awareness, discrimination, memory and learning. Under some circumstances, widespread deficits in these integrative functions produce varied degrees of delirium; in its full extent this is a state of restlessness, confusion and disorientation, usually also

*In this respect the reticular activating system resembles the "Old Oxroad" of the popular song, conceded to be "not a place but just a proposition."

with hallucinations (6). Hence, it is not unexpected that, when coma develops in a diffuse cerebral disorder, the patient may exhibit some of the features of delirium as consciousness is gradually lost and perhaps also as it is regained. In contrast, when coma results from a focal lesion restricted largely to the reticular activating system, delirium is not likely.

Brain Metabolism

Since many disorders leading to coma are metabolic in nature, brief consideration is here given to the basic principles of brain metabolism. The importance to the brain of two basic foodstuffs—oxygen and glucose—is a familiar fact. Recent evidence suggests that neurons may be more vulnerable than usual to hypoxia after a period of intense excitation and more resistant under hypothermic conditions, points of special clinical interest (6, 7). Biochemical derangements of other types also affect the brain, including those of carbon dioxide, electrolyte, protein (notably glutamine) and lipid metabolism, but the nature of these effects has thus far not been determined by precise study (8, 9).

Delivery of essential substances to the brain is measurable by modern methods for determining cerebral blood flow. These technics are limited in scope since they cannot define minor, brief or localized alterations in circulation or oxygen uptake. In general, cerebral oxygen consumption falls but total cerebral blood flow is little altered when brain metabolism is disordered by depletion of blood sugar, by diabetic ketosis, by vitamin B_{12} deficiency or by the action of various narcotic drugs. In contrast, in hypothyroidism both cerebral circulation and cerebral oxygen utilization are reduced.

Occlusive disease of arteries of the brain is a threat to areas supplied by the diseased vessels, particularly when collateral channels are inadequate in number or size. A damaging degree of hypoxia may result despite maximal oxygen extraction and even though total cerebral blood flow may remain within normal limits (9).

The impairments of neuronal function associated with extremely high or low body temperatures are of unknown nature and undoubtedly complex, involving multiple enzyme systems.

Causes of Coma

It is reasonable, in theory, to divide the causes of coma into two broad groups: those which act primarily by interference with the ascending activating system and lie deep in, close to the core of, the brain, and those which act more diffusely, involving in particular cerebral cortical functions. In actual practice, however, a clear distinction between the two mechanisms is often impossible. In some patients both mechanisms may operate from the onset, as with concussive head injury or encephalitis, and in others one mechanism may ultimately be reinforced by the other, as in the patient with an expanding, deep midline tumor. A more practical scheme, derived in large part from that of McDowell and Wolff (10), is attempted in Table 2 describing the various intracranial, systemic and generalized disorders which may account for coma.

It is apparent that special clues to illnesses in group I are found in a detailed general and neurologic survey, x-rays of the head, electroencephalogram and, when warranted, examination of the spinal fluid for pressure, appearance, cell count, protein and sugar determinations and serologic reaction. Recognition of the disorders within the remaining groups hinges directly on an adequate history and general examination, supplemented by selected laboratory studies of various organ functions, e.g., complete blood counts, urinalysis, electrocardiogram and appropriate blood chemical determinations.

The commonest causes of coma in the experience of a large city hospital before the modern period of effective antimicrobial therapy were head injury and intracranial vascular disease, both carrying high mortality rates (11). Alcoholism and other forms of poisoning were also frequently encountered but were seldom fatal. In one autopsied series of patients, the accuracy of antemortem diagnosis was found to have been no better than 50%.

Conditions Which May Be Mistaken for Coma

At this point it is well to call attention to common and uncommon disorders which superficially simulate the comatose state but which on close inspection can usually be distinguished from it.

TABLE 2.—MAJOR CAUSES OF COMA

I. Primarily intracranial disorders
   A. Local derangements in circulation
      1. Thrombosis, embolism or parenchymal hemorrhage
      2. Primary subarachnoid hemorrhage
   B. Head injuries
      1. Brain concussion, contusion or laceration
      2. Hemorrhage (epidural, subdural or parenchymal)
   C. Infections
      Encephalitis (viral, bacterial, rickettsial or mycotic), with or without meningitis
   D. Expanding masses
      1. Tumor (primary or metastatic)
      2. Abscess
      3. Hematoma (including those of *A* and *B*)
   E. Epileptic illnesses
      1. Postictal states
      2. Status epilepticus
II. General disorders of circulation and oxygen supply
   A. Severe hypotension
      1. Blood loss by hemorrhage
      2. Myocardial infarction
      3. Systemic infection causing toxemia (as in the Waterhouse-Friderichsen syndrome)
      4. Other causes of shock
   B. Severe congestive heart failure (sometimes with pulmonary insufficiency), mainly in the aged
   C. Hypertensive encephalopathy
   D. Asphyxia of various sources
III. Endogenous intoxication and metabolic disorders
   A. Severe systemic infection
   B. Hepatic failure
   C. Hypoglycemia
   D. Diabetic ketosis
   E. Renal failure (azotemia)
   F. Adrenal failure
   G. Hyperthyroid crisis
   H. Hypothyroidism
   I. Electrolyte derangements (mainly involving sodium)
   J. Eclampsia
   K. Vitamin deficiency of the B group
IV. Exogenous intoxications
   A. Excess of ethyl alcohol
   B. Excess of various medications of sedative, "tranquilizing," anticonvulsive or analgesic nature
   C. Carbon monoxide
   D. Heavy metals (mainly lead)
V. Electric shock
VI. Severe hyper- or hypothermia

Perhaps most important are the "trance states," ranging from apparent stupor to apparent coma, which are part of *primary psychologic reactions,* sometimes profound in degree. It is arguable that in these illnesses, even though there be no demonstrable lesion in the structures essential to wakefulness, there is in some way a disorganization of function sufficient actually to reproduce stupor or coma. Certain features in the behavior of the affected patients, however, indicate that the derangements in function are of a very special sort. The electroencephalogram record is one of normal wakefulness. Caloric stimulation of either ear by cold water instilled into the external canal will induce a normal ocular response—nystagmus with a quick phase to the opposite side—whereas in true coma such stimulation is likely to induce either abnormal ocular patterns or no response at all. A relatively benign form of trance is that which occurs in some dissociative reactions, apparently representing a defense against intolerable anxiety. The state may be brief or prolonged, commonly develops under circumstances promoting emotional tensions and may be recurrent. Fluttering of the eyelids, hyperventilation and rapid recovery of full awareness are useful but not infallible diagnostic clues. It is sometimes evident that the victim retains many of the cognitive functions despite his apparent lack of awareness. Although he may describe complete amnesia for the episode, under the influence of induced narcosis, as with amobarbital, he may recall in detail what transpired while he was "unconscious."

More ominous in significance are certain states of apparent unconsciousness, sometimes long-lasting, resulting from profound disorders of a psychotic nature, as exemplified by the "stupor" of catatonic schizophrenia. The antecedent history and bizarre posturing of the limbs usually identify the general nature of these illnesses. It is unfortunately true, however, that in rare instances the clinical picture of catatonia results from structural brain disease, usually deep or extensive; it is then combined with abundant other neurologic signs of diagnostic aid; these, together with the full history, point to the nature of the problem.

Rare, but of particular interest and curious nature, is the condition described by Cairns (12) as *"akinetic mutism."* This has been encountered in a few patients with lesions in the upper brain stem, diencephalon or anterior cingulate gyri, above the

corpus callosum. In this syndrome the patient is silent and virtually immobile, appearing unconscious on brief inspection yet at least partly aware and often able to withdraw from noxious stimuli. Other neurologic signs are likely to be present to aid in localizing the lesion. If the cause is partly reversible, as by surgical treatment, the patient may quickly rouse to full activity, although unable to recall the period of inertness.

A clear description of this state, as observed in a patient with a suprasellar cyst, has been given by Cairns (12):

> The patient was a girl of 14 with an epidermoid cyst distending the region of her third ventricle. In the fully developed state she lay inert, except that her eyes followed the movement of objects or could be diverted by sound. As one approached the bedside her steady gaze seemed to promise speech, but no sound could be obtained from her by any form of stimulus. A painful stimulus would produce reflex withdrawal of the limb and, if the stimulus was maintained, slow feeble ineffective movements of a voluntary kind to remove the source of stimulation, but without tears, noise or other signs of pain or displeasure. She swallowed readily, but had to be fed; hard food would be swallowed whole and she would take sugar, salt or quinine in her mouth without any sign of pleasure or distaste. There were also mild signs of bilateral pyramidal tract involvement, and she was totally incontinent of urine and feces.

Akinetic mutism is not a pure syndrome. It may occur in partial form or in association with numerous other neurologic deficits, dependent upon the location and extent of the underlying cause. Its differentiation from actual stupor or coma is more of theoretical interest than practical value.

Less likely to be misinterpreted as unconsciousness are the brain disorders resulting in *global aphasia*. The victims are mute or utter only senseless noises and show no understanding of commands. They usually can fix their gaze on the examiner and respond to various forms of visual, auditory, tactile or noxious stimulation, indicating perception, if not comprehension. In almost every instance the aphasia, denoting a lesion of considerable size in the middle third of the dominant hemisphere (usually the left), is accompanied by an obvious contralateral hemiparesis or hemiplegia. If the damage develops acutely, as with a major arterial occlusion or hemorrhage, stupor or coma may well be the initial manifestation, the aphasia coming to light only if and when consciousness returns.

An *epileptic attack of psychomotor type* is generally recurrent and is so distinctive a seizure that its special meaning is soon apparent. In a few patients, however, the attacks are marked mainly by arrest of all activity, with little or no unusual movements or speech. Full recovery ordinarily occurs within a few minutes, after a transitional phase of confusion. Of quite different significance is the period of complete unresponsiveness which exists briefly at the end of a convulsion or other major epileptic attack or which persists throughout status epilepticus. These postictal or interictal states are true forms of coma.

Finally worth mention are the situations of the past *erroneously identified in retrospect* as coma, based on incomplete clinical data. Such misleading information is commonly found in the taking of a medical history. Looking back, the individual unwittingly reports that some months or years ago he was "unconscious for several days" following an injury or with a severe infection. When more information is obtained from his relatives and his physician, it becomes evident that the clinical state was one of confusion or frank delirium, often either post-concussional, toxic-infectious or drug-induced, for which he has no memory. In short, his prolonged "coma" turns out to have been a period of amnesia, during which he may have been addled but clearly was not unconscious.

GENERAL MANAGEMENT OF THE COMATOSE PATIENT

When consciousness is lost in the natural evolution of a known disease, no special problems in diagnosis or therapy arise. All too often the process is then beyond any help the physician can offer. When, on the other hand, coma develops unexpectedly, especially if the patient is deposited in an unresponsive state in the physician's office or the hospital emergency room, prompt attention is called for. Frantic concern of relatives and the manifold uncertainties of the clinical problem may hamper the examining physician but should not block a well directed program for action. The strategic principles are clearly presented in recent reviews by McDowell and Wolff (10) and by Adams (11), including the following steps:

THE PRESERVATION OF VITAL FUNCTIONS.—This must be undertaken immediately, even while the cause of the coma remains

uncertain, lest irremediable brain damage occur. To this end the physician must combine speed with cool reflection. He should not allow himself to be pushed into premature action. His guiding maxim might well be an inversion of a familiar exhortation: "Don't just do something, stand there"—and think. After a preliminary appraisal he can organize his plan of procedure. He is then prepared to move sensibly ahead. In particular, attention should be given to three possible dangers:

1. The state of the *circulation* may be threatened by severe hypotension, usually a sign of bodily injury, external or hidden bleeding, a myocardial infarction or, rarely, a primary central nervous system lesion. If the blood pressure is even moderately depressed, an intravenous infusion should be started so that if dangerous hypotension develops pressor agents (such as levarterenol or metaraminol) or plasma can be quickly given. Sites of visible bleeding should receive immediate attention to halt blood loss.

2. The state of the *airway* is checked for obstruction by direct inspection of the mouth and tongue and by observation for stridor, flaring of the alae nasi, retraction of the intercostal spaces, or increased rate and decreased volume of air exchange. If the tongue has fallen back, it should be pulled forward and the patient turned onto his side. Suctioning of the mouth and trachea is warranted if excess mucus or vomitus is present. An endotracheal tube is placed if necessary or a tracheotomy tube is inserted, and if ventilation is still inadequate, assistance is given either by a positive pressure device connected with the tube or by a tank respirator.

3. The state of the *blood sugar level* is assessed in a preliminary way by an immediate inquiry as to whether insulin or similar medications could be at fault. Even the slight possibility that hypoglycemia exists justifies removal at once of a specimen of blood for sugar measurement and the prompt administration of glucose by slow intravenous injection, preferably at least 10 Gm. (in 20% solution).

THE COLLECTION OF HISTORICAL DATA.—Pure speculation as to the origins of the illness, unsupported by any reliable data, is likely to be fruitless. Since the patient himself, the obvious source, is inaccessible to questioning, contact should be made at once with whoever came with the patient, or with relatives

and friends at home or elsewhere. The aid of the police and other physicians can sometimes be enlisted. These efforts can be begun even while emergency care is underway. Of special importance are inquiries about immediately antecedent injury, ingestion of drugs, seizures, fever or other signs of infection. If the past history can be obtained, it should be reviewed quickly with reference to hypertension, bleeding tendencies, angina, myocardial infarction, diabetes, epileptic disorders, hepatic or renal disease, or major psychiatric illness.

THE SYSTEMATIC EXAMINATION OF THE PATIENT.—This step is carried out deliberately and as completely as possible, within the limits imposed by the patient's obtunded state. Data already at hand probably have reduced the number of possible diagnoses and point to one or several likely choices. The examiner should search with special care for signs of these disorders. In addition he should be guided by the hope that he may find a treatable cause for the illness. Hence, he must look closely for indications of any of the following *common reversible conditions:* drug intoxication; intracranial but extracerebral hematomas (epidural or subdural); intracranial infections (brain abscess, bacterial or mycotic meningitis); systemic infections with severe toxemia (perhaps also with hypotension); hypoglycemia; and diabetic ketosis.

The preliminary observations of vital signs, together with whatever clues have turned up in the available history, offer guides in the next step, a general physical examination. In this, particular emphasis should be placed on those maneuvers most pertinent to the principal diagnostic possibilities. A useful but often forgotten procedure at the outset is to give a full 3 minutes to deliberate inspection of the patient's color, posture, spontaneous movements and breathing pattern. Kussmaul breathing (deep and rapid), suggestive of acidosis, and Cheyne-Stokes breathing (periods of hyperpnea alternating with apnea), suggestive of brain stem damage, are of special diagnostic value. The odor of alcohol on the patient's breath is an important finding but does not necessarily establish the diagnosis, for the coma may stem from some complicating development, notably head injury or overwhelming infection, to which the alcoholic patient is notoriously prone.

If there is a possibility of trauma, care must be taken to avoid further injury, especially to the cervical spine. When coma is due to a recent head injury, there are usually external signs of damage to the face or scalp. Yet a subdural hematoma may treacherously cause no trouble until many days or weeks after the original superficial injuries have healed and, particularly in the aged, may occur after a head blow so trivial as to leave no external sign.

Fever suggests infection, heat stroke, intracranial bleeding or acute injury deep within the brain. A low body temperature raises the possibility of drug intoxication (especially alcohol or barbiturate), myxedema or shock. The combination of fever and stiff neck in a comatose individual is ominous, usually denoting meningeal bleeding or infection, although these signs sometimes accompany severe infarction of the brain with normal spinal fluid. Conversely, nuchal rigidity may disappear when coma becomes very deep.

The degree of unconsciousness must be estimated early in the survey, mainly by observation for any apparently purposeful movements, changing facial expression or eye position, and responses to visual, auditory (including verbal) and painful stimuli. A test of deep pain sensibility, as by squeezing a muscle, large tendon or testis, is particularly effective in separating shallow from deep coma.

The rest of the neurologic portion of the examination is necessarily limited, but many indirect clues may be found which point to a local brain lesion if such be present. Examination of the optic fundi is essential, mainly in search of choked discs, the subhyaloid hemorrhages suggestive of subarachnoid bleeding, or retinal vascular disease. In the stuporous patient the visual fields can sometimes be grossly tested by observing the blink reaction to a threatening gesture from each side. Inequality in pupillary size is a helpful but not always a localizing sign. The unilateral widely dilated and fixed pupil sometimes signifies an acutely expanding lesion on the same side within the skull, producing a temporal lobe herniation through the tentorial opening, as may occur with an extradural hemorrhage.

Focal motor seizures are of obvious lateralizing value, as also are indications of a hemiparesis, as inferred from ballooning of one cheek in expiration or a unilateral lack of restless move-

ments or of withdrawal from noxious stimuli. The deep reflexes are usually depressed on the side of a recent hemiparesis, later becoming hyperactive. Sustained conjugate deviation of the eyes suggests a lesion in the frontal lobe toward which the gaze is directed or in the opposite pons. When both pupils are dilated and fixed to light, when the corneal reflexes are absent and Babinski signs are present in both feet, severe and extensive brain damage is evident, often irreparable, regardless of cause.

Laboratory procedures are of secondary importance in the initial phase of the diagnosis, but each patient should soon have a complete blood count and urinalysis. When poisoning is suspected, stomach contents obtained by nasogastric tube should be saved for later analysis. The urine examination is of special value in renal failure or diabetic ketosis, but it should be noted that proteinuria may temporarily follow febrile illnesses or subarachnoid hemorrhage, and that glycosuria secondary to hyperglycemia may result from acute and massive cerebral damage. Chemical determinations on venous blood are made for glucose, non-protein or blood urea nitrogen, sodium, potassium, chloride and carbon dioxide whenever the diagnosis is unclear or when derangements in any of these values might complicate the illness and require specific treatment.

A lumbar puncture is never a routine matter but should be carried out as soon as possible, unless the diagnosis is already established and this test is either unnecessary or unduly hazardous. The procedure should be planned with care to provide the maximum of information and minimum of misinformation, for it offers ample opportunities for omission of crucial data and the recording of erroneous results. The test should always include a record of the appearance and pressure of the fluid and the cell counts and protein content. The jugular compression maneuver is neither useful nor wise and should be omitted. If the first sample of fluid is blood-tinged or frankly bloody, it is essential to know whether the discoloration lessens as more fluid is drawn off (indicating a traumatic tap) and, if all samples are equally bloody, whether the supernatant is yellow after centrifugation (indicating that bleeding had occurred at least several hours before the tap). When the white cell count of the spinal fluid is elevated, a determination of the content of sugar (combined with a blood sugar measurement at the same time) and

arrangements for culture should be made. If the pleocytosis is mild or moderate, e.g., less than 500 per mm.^{3}, the culture technics should include media for detecting tubercle bacilli and fungi.

X-rays of the skull are desirable whenever head trauma or an expanding intracranial mass is suspected. A chest x-ray should be a routine measure. The patient with possible or proved heart disease merits an electrocardiogram. An electroencephalogram is rarely needed early in the study but contributes much to later observations of the course of the illness and is sometimes of special value in confirming what is suspected of being entirely a psychologic reaction.

GENERAL PRINCIPLES FOR THE CONTINUING CARE OF THE PATIENT.—After the initial survey, emergency measures, full examination and diagnostic procedures are completed, the physician must arrange a program of management. Numerous problems are likely to arise, particularly when it is foreseen that the coma may endure for a prolonged period. Quite apart from whatever is done for the patient is the importance of a systematic plan for following his clinical state from day to day. Progression or regression in the degree of unconsciousness must be estimated at regular intervals in terms of his general behavior, his pupillary, corneal, pharyngeal, tendon and plantar reflexes, and his reactions to noxious stimulation. Equally important is a charting at appropriate intervals of the blood pressure, pulse and respiratory rates, rectal temperature, fluid intake and output and body weight. It is helpful to select certain of the most meaningful data and arrange these in tabular form on a separate sheet in the clinical record, to which ready reference can be made each day.

Continued attention is obviously necessary to respiratory and circulatory functions, especially if problems with these were present from the start, as outlined in an earlier section. Until the patient's gag and cough reflexes are effective, he should be placed much of the time in the semiprone position. A suction apparatus should be available. Humidified oxygen can be administered when necessary by mask at frequent intervals. If assisted respiration is necessary for a long period, because of weakness of the muscles of breathing, a tank respirator is best. To maintain adequate nutrition a gastric tube can be used but

need not be inserted until the acute phase of the illness is over. The tube-feeding mixture should not be unduly large in volume or high protein content and should contain vitamin supplements. Particular care is necessary in adjustments of fluid and electrolyte intake, checked by observation of skin turgor, body weight and urine output, and by blood chemical determinations. A retention catheter should be inserted if the patient cannot void. High fever justifies cooling sponge baths and removal of blankets.

A major nursing aim is prevention of bed sores and requires frequent turning of the patient, meticulous skin care and precautions that the sheet on which the patient lies is free of folds or wrinkles. Side rails should be on the bed at all times and a vertical board placed at the foot, against which the patient's feet can rest in neutral position as much of the time as possible. If he becomes agitated, confused or delirious, it is far better to have an attendant constantly by his bed than to use mechanical restraints. Whenever possible the attendant should be a relative or friend. In long-term incapacity, the assistance of the physiotherapist should soon be enlisted to prevent contractures.

The prophylactic use of antibiotics is generally unwise. These agents are best reserved for the treatment of specific infections that may arise.

Details of therapy in addition to the above depend upon the underlying cause and anticipated course of the illness. These are the concern of the following section.

DIAGNOSIS AND TREATMENT OF CERTAIN MAJOR CAUSES OF COMA

To consider in detail the diagnostic and therapeutic aspects of the many causes of coma would carry the reader far afield. It is more reasonable to select for brief discussion the clinical entities of particular importance or interest, stressing what is new in concept and practice.

Derangements in Intracranial Circulation

This category holds the principal varieties of "stroke." When damage from thrombosis, embolism or hemorrhage into the substance of the brain is so severe as to lead to more than brief

unconsciousness, precise anatomic diagnosis is largely an academic exercise. In most instances little can be done in the way of definitive therapy other than to conserve vital functions and wait for whatever repair may occur. Once a major infarct has occurred, anticoagulation offers little advantage and entails appreciable risk. Evacuation of an intracerebral hematoma in a comatose patient is rarely worth attempting. Hypothermic therapy may halt a downhill course but probably has little effect on the ultimate outcome of the illness.

Subarachnoid hemorrhage, however, calls for more active measures. It almost always arises from rupture of an aneurysm on or near the circle of Willis and usually presents a characteristic clinical picture of sudden intense headache, followed by nausea, weakness, stiff neck, and often fever and focal neurologic signs. Coma supervenes in perhaps one-third of the patients and is then a grave prognostic sign. Although the diagnosis is apparent in the typical illness, examination of the spinal fluid should never be omitted, lest an acute infectious meningitis be overlooked. Unless the patient is moribund, bilateral carotid arteriograms are warranted early in the attack. If no aneurysm is demonstrated, vertebral arteriograms may be considered. The decision should be guided by local experience with this more difficult technical procedure. The finding of one or more aneurysms poses a difficult question for the neurosurgeon, who must select the most feasible method of surgical treatment. Cooperative clinical studies in this country and abroad are now seeking better answers to this problem.

Head Injuries

Acute head injury presents an equally troublesome situation, for when coma results the extent of brain damage is estimated with difficulty, and the indications for operative treatment may be changing and uncertain. Unconsciousness beginning with the head blow and lasting over an hour almost certainly denotes more than a pure concussion. It has been suggested that one mechanism for sustained unconsciousness after head injury is extensive spasm of anchoring arteries secondary to the abrupt displacement of the brain, but proof is lacking (13). Better known and proved causes are contusion or laceration of the brain

or bleeding into the epidural or subdural space. Epidural hemorrhage, in particular, should be suspected when x-rays reveal a skull fracture passing through a major vascular channel, such as that of the middle meningeal artery, or when, after a post-accident lucid interval of minutes or several hours, the patient enters a deepening coma. With this may also develop dilatation of the pupil on the side of the bleeding and a contralateral hemiparesis. Immediate surgical intervention is essential.

Subdural hemorrhage is likely to be subtler and more variable in tempo. When it develops early in the illness it is usually associated with laceration of the uderlying brain; the latter lesion may be the more decisive one and the cause of coma from the outset, concealing the development of the hematoma. Dott's comment (13) is directly relevant: "I know of no clinical problem more difficult than the diagnosis of a secondary, expanding, displacing process in a patient who is still unconscious from the initial concussion." In this situation exploratory burr holes are usually justified.

It is of physiologic interest that after a severe head injury acetylcholine may enter the spinal fluid in minute but measurable amounts, sometimes persisting for several days. This agent is presumably released from concussed or otherwise altered brain tissue. There is no direct evidence that the presence of acetylcholine within the spinal fluid has adverse effects or that the administration of atropine, which has been tried in a few patients, significantly eases symptoms or promotes recovery.

Derangements in water and salt metabolism may quickly follow severe brain trauma (14). The alterations are of various kinds, perhaps most often the result of injudicious treatment with hypotonic solutions (as discussed in a later section). Hypernatremia in some patients with severe cerebral or hypothalamic damage may represent a disorder in osmoregulatory systems but is usually short in duration if an adequate fluid intake is provided.

A sustained rise in intracranial pressure is a serious complication. It follows various forms of cerebral damage and commonly denotes edema. In this situation the administration of hypertonic urea is often of immediate benefit, especially when a craniotomy is contemplated. Urea is customarily given by intravenous infusion in 30% concentration in invert sugar (Urevert) in amounts

of 1.0–1.5 Gm./kg. of body weight. It can be repeated once or twice each day when effective and necessary. A brief rebound rise in spinal fluid pressure to above the pre-injection level occurs in some patients but urea is generally safe, except for patients with renal insufficiency. Transient hemoglobinuria is a sequel to treatment in rare instances (15).

The family of the brain-injured patient inevitably seek assurance as to the degree of his recovery. Prediction must be guarded, but it is clear that prolonged unconsciousness is ominous for future performance. If coma persists a month or more, permanent invalidism due to major neurologic deficits (including mentation) is likely, if the patient survives at all. In general, the young have faster and more complete recoveries than the elderly.

Intracranial Infection

The patient with general and spinal fluid signs of meningitis who enters a coma has more than meningeal infection. Brain substance is also affected, in some instances via lesions of entering vessels, and in both clinical and pathologic terms he has a meningoencephalitis.

The chief goal in the diagnostic study is the detection when possible of an organism susceptible to specific counterattack. An etiologic diagnosis is often hampered by the fact that the patient recently received an antibiotic agent in amounts sufficient to modify the signs and laboratory data yet inadequate to eliminate the infection. The illness may therefore resemble a viral infection, for the spinal fluid cell count may be only slightly increased, with mononuclear cells predominating, and the culture may be sterile. Nonetheless, the physician is usually then committed to continue antimicrobial therapy, preferably with a broad-spectrum antibiotic, hopeful but uncertain that his treatment plan is appropriate.

Chronic Pulmonary Insufficiency

Advanced chronic pulmonary disease, as results most commonly from emphysema and fibrosis of the lungs, may lead to progressive impairment of consciousness. The neurologic signs include also various degrees of tremor and, in a minority, convulsions. A few patients develop frank papilledema.

The primary mechanism is one of carbon dioxide retention, but hypoxia may contribute a large share to the brain malfunction when congestive heart failure or respiratory infection develops as well (16). The hypercapnia may be aggravated by the administration of narcotic drugs. Even more characteristically the symptoms are made worse by oxygen therapy, for the medullary respiratory center, relatively insensitive to blood CO_2 tension in these patients, is driven mainly by low oxygen tension. If this stimulus is weakened by oxygen administration, respiratory exchange falls and CO_2 retention and acidosis are augmented.

Heart failure, if present, is managed in the usual ways. Phlebotomy proves useful if secondary polycythemia is found, and any pulmonary infection is treated with antibiotics and bronchodilators. Mechanical aids to respiration may be necessary to carry the patient through a crisis.

Hepatic Failure with Shunt Encephalopathy

The most intriguing complications of liver failure are those comprising "hepatic (shunt) encephalopathy." This syndrome has been intensively studied in clinical laboratories during the past decade, for the manifestations are striking and the mechanisms only partly explained. The neurologic picture is highly varied and may develop rapidly in acute hepatic injury or slowly and most irregularly with chronic illness (17). In addition to impairments in consciousness of mild to severe degree, there may be fluctuating rigidity, exaggerated deep reflexes and, in late stages, extensor plantar responses. A prominent feature is a peculiar, slow, coarse and nonrhythmic, "flapping" tremor of the outstretched arms.

The disorder is manifestly metabolic in origin. The impairment of liver function, as determined by usual tests, need not be marked, for the key deficit is one of abnormal delivery of blood—a shunt from the portal veins directly into the systemic circulation via the vena caval system. This may result not only from high portal pressure of liver disease, notably cirrhosis, but also from operations for ascites or esophageal varices. Toxic products of digestion and of bacterial action in the intestines, e.g., ammonia, enter the general circulation directly, escaping the protective functions

of the liver. Hence the well-recognized intolerance of nitrogenous foods reported by many patients with incipient or recurrent shunt encephalopathy.*

An elevation in blood ammonia is commonly found when the encephalopathy develops, but there is no direct quantitative relationship between the chemical and the clinical findings. Other toxic substances as yet unidentified undoubtedly contribute to the brain disorder. Stupor or coma may be precipitated, not only by a high protein intake, but also by treatment with chlorothiazide (Diuril) or acetazolamide (Diamox). Depletion of electrolytes, particularly sodium, potassium or magnesium, readily worsens the encephalopathy. Although alkalosis is prominent in many seriously ill patients, apparently as a result of hyperventilation, it has been shown that the administration of carbon dioxide by inhalation has adverse effects (19).

Treatment should include a diet restricted in protein, with no more than 20–30 Gm. per day. In comatose states ample glucose must be given by infusion plus correction of whatever electrolyte deficiencies are found. Breakdown of protein by intestinal bacteria is lessened by neomycin sulfate, given orally in 1.0 Gm. amounts hourly for 4 hours, then every 4–6 hours for several days, and then perhaps twice daily indefinitely. Variable benefit has been reported from the intravenous infusion of sodium or potassium glutamate or of arginine hydrochloride. Hemodialysis has had limited trial but with favorable results.

Hypoglycemia

A fall in blood sugar sufficient to produce coma is an uncommon event. Although spontaneous improvement usually occurs through automatic protective devices within the body, this may be delayed until after irreparable brain damage has been produced. An excessive dose of insulin in the diabetic, combined with omission of a subsequent meal, is readily suspected from even a limited history, but the presence of an islet cell tumor of the

*Summerskill (18) has suggested that this phenomenon explains some of the erratic behavior of Shakespeare's Sir Andrew Aguecheek. The knight himself observes: "Methinks sometimes I have no more wit than a Christian or an ordinary man has, but I am a great eater of beef, and I believe that does harm to my wit."—*Twelfth Night,* Act I, scene 3.

pancreas, the other main cause, may not at first be apparent. The histories of patients with such insulin-producing tumors are widely varied. Their symptoms are episodic, occurring usually before breakfast or after a meal has been skipped. Giddiness and sweating are the commonest prodromes. A misleading feature in some patients is the occurrence of asymmetrical symptoms and signs, such as a unilateral tremor or weakness. The full hypoglycemic reaction includes confusion or bizarre episodes resembling psychomotor seizures. Generalized convulsions or coma are less likely to occur.

Diagnosis and appropriate treatment, obviously beginning with the rapid administration of glucose, are not difficult once the nature of the problem is suspected, and hepatic, pituitary and adrenal causes of hypoglycemia are ruled out.

Hypothyroidism

The onset of coma in myxedema is a rare and usually a terminal event, associated with cardiac, pulmonary or renal complications (20). The progress of the disease may be so slow and insidious that it remains undiagnosed and untreated until close to its end. Women are affected more often than men. Grand mal seizures sometimes directly precede the decline into coma, indicating the extent of the metabolic brain damage. Almost all patients are hypothermic, some strikingly so, yet they do not shiver. The classical signs of myxedema are usually apparent. A mild to moderate anemia and mild azotemia, hyponatremia and hyperkalemia are commonly associated. Carbon dioxide retention occurs in some instances, aggravating the brain disorder.

Replacement therapy must be prompt and vigorous, even when heart failure coexists. It can start with triiodothyronine by parenteral route. Body temperature should be gradually elevated to a near-normal level and, if hypercapnia is found by arterial blood analysis, artificial respiration should be instituted.

Electrolyte Derangements

Many of the disorders in concentration of crucial electrolytes found in the comatose patient are secondary to his total illness and not prime causes of his unconsciousness. Yet, as mentioned

in the discussion of head injuries, they may readily complicate an already hazardous situation. They demand early recognition and correction.

Hypernatremia and hyperchloremia may easily develop in the unconscious individual who is inadequately supplied with fluids or treated too enthusiastically with osmotic diuretics such as urea or high-protein tube feedings. Other causes are unrecognized diabetes insipidus, hyperventilation and some forms of brain injury.

Sodium depletion, sometimes masked at first by concurrent water loss, should be suspected in many different circumstances, most commonly with protracted vomiting or diarrhea, excessive sweating, certain forms of renal disease, some brain injuries, diabetic ketosis overtreated with glucose and fluids, adrenocortical insufficiency, cirrhosis, and cachexia and malnutrition. It is a major feature, also, of water intoxication.

Hyperkalemia occurs with coma perhaps most commonly in renal failure. Potassium depletion, on the other hand, may result in many of the sodium-losing states already listed, except in adrenocortical insufficiency. It is often accompanied by hypochloremic alkalosis, with an increase in plasma carbon dioxide combining power.

Magnesium deficiency is less often recognized and sometimes is of uncertain significance, for it usually coexists with other major derangements of the electrolytes (21). The symptoms include tremor or other abnormal movements, delirium, confusion and, rarely, convulsions. They may appear in patients with malnutrition of any cause, and particularly in association with cirrhosis or chronic alcoholism.

Alert to these various possibilities, the physician caring for a comatose patient can soon detect and in part, at least, correct whatever electrolyte imbalance he finds. Parenteral replacement of the deficient substances may be necessary at first, but a shift to the oral route should be made as soon as possible. The principles underlying the actual calculation of fluid and electrolyte needs will not be reviewed here.

Exogenous Intoxication

Most of the coma-producing poisons of the present day are drugs taken to excess, in error or deliberately. In many instances

the precise nature of the medication is unknown when the patient is first seen, but this need not delay immediate supportive care, as outlined in an earlier section. If it is suspected that a poison has been ingested, attempts should be made to empty the stomach by gastric lavage unless there is visible evidence within the mouth that strongly caustic agents have been swallowed. It is unwise to stimulate vomiting in the unconscious patient by pharyngeal stimulation or administration of gastric irritants or apomorphine. A saline cathartic can be left in the stomach after lavage to hasten evacuation of any poison remaining within the gastrointestinal tract.

Experience with hemodialysis by the artificial kidney is now extensive. It is probably desirable to consider this form of treatment whenever the patient is or may be severely poisoned and the offending agent is dialyzable. The coma-producing poisons which in theory or practice can be removed from the blood by dialysis are: barbiturates (particularly phenobarbital), bromide, salicylate, glutethimide (Doriden), ethinylcyclohexyl carbonate (Valmid) and ethylene glycol (22). Others will undoubtedly be added to the list in time. Toxicologic studies may be important but are rarely possible early in the illness.

Certain common forms of intoxication merit specific discussion. *Acute alcoholism* sufficient to lead to coma is readily recognized from the general appearance of the patient and the odor which envelops him, but it is essential not to overlook some other cause for his unconscious state, such as head injury or infection. Suspicion of such possibilities is raised, in particular, if the blood alcohol level is under 200 mg./100 ml. If vital functions are preserved, the patient will almost always emerge from his experience undamaged and, at times, unrepentant.

The *barbiturates* are common sedative poisons and as causes of coma by far surpass the bromides. Barbiturate blood levels offer only approximate guides to the degree of intoxication, for the chemical test does not differentiate between short- and long-acting agents. Stupor or coma from a short-acting barbiturate, such as pentobarbital, usually requires a blood level of over 1 mg./100 ml., whereas for a long-acting form, such as phenobarbital, the level is over 5 mg./100 ml. The therapeutic value of cortical stimulants in shortening the coma is a matter of controversy. Such analeptics as picrotoxin and pentamethylente-

trazol (Metrazol) have had extensive trial, but many authors contend that they drive a sick brain too forcefully and add little to the outcome. Favorable results have recently been reported from several newer agents, including bemegride (Megimide) and 2,4 diamino-5-phenylthiazole (Daptazole), both described as safe barbiturate antagonists and stimulants.

The almost innumerable *tranquilizers* (ataractics) are less dangerous in general and rarely cause irreversible coma. Severe hypotension may result from meprobamate or certain of the phenothiazine derivatives, and restlessness, occasionally also convulsions, may develop as the patient begins to rouse.

Salicylates rank high in danger to children, who so often have access to flavored preparations of aspirin. Hyperventilation leads often to a respiratory alkalosis and hypokalemia, but may later be replaced by a metabolic acidosis for which specific corrective measures are needed.

Intoxication with *atropine* or other agents of the belladonna group is usually distinctive and dramatic. The cardinal features are those of parasympathetic blockade and include initial excitation and later, in severe poisoning, circulatory collapse and coma. The clinical picture has been described as "hot as a hare, red as a beet, dry as a bone, blind as a bat and mad as a wet hen." A remarkable sensitivity to such reactions has been noted in a few children treated merely with atropine or homatropine eye drops (23). Specific antagonists, such as pilocarpine or methacholine, are reported to be of little benefit when atropine poisoning is severe.

Lead poisoning occasionally leads to coma, chiefly in infants and children. The illness commonly may be precipitated, after chronic ingestion of the poison, by an intercurrent illness producing acidosis. Convulsions, generalized or focal, and signs of increased intracranial pressure are common. Anemia, basophilic stippling of the red blood cells, and an elevation of spinal-fluid protein content are other particularly useful diagnostic clues. Treatment of this encephalopathy is difficult. Benefit has been noted in some patients from the use of the chelating agent edathamil calcium-disodium (Calcium Disodium Versenate), given by intravenous infusions (24).

Hypothermia

Profound depression of body temperature to levels below 30° C. (86° F.), as measured in deep body zones, leads to stupor or coma, striking bradycardia and susceptibility to cardiac arrhythmias. Apart from its use as an aid to surgery or in a few other clinical situations, hypothermia of this degree is rarely encountered. It may follow immersion in chilling water, however, or exposure to cold air, especially when the subject is intoxicated. The primary diagnosis presents no difficulty, for it is made by history and touch. A major problem concerns how best to raise body temperature to normal (one purpose of the infamous experiments with concentration-camp victims in World War II). Careful experiment and clinical observation now make it clear that, as least in acute hypothermia, the proper procedure is to warm the patient either rapidly (as by a water bath at 45° C.) or very slowly. The middle course is unwise, permitting a dangerous circulatory failure from peripheral vasodilatation and excessive diversion of blood to outlying areas.

SUMMARY

The cerebral cortex and deep-lying structures extending down into the brain stem work together in the maintenance of the wakeful state. Depression of consciousness, of which coma is the ultimate stage short of death, can result from various kinds of structural, metabolic and toxic damage to these vital systems.

Cerebrovascular accidents (strokes), head injury and drug poisoning predominate among the causes of unexpected unconsciousness.

Care of the comatose patient starts with close attention to the respiratory, circulatory and metabolic activities immediately essential to survival, even before the full explanation for his plight is uncovered and specific treatment begun. The principal useful tools are: the intravenous infusion set, nasogastric tube, catheter, sphygmomanometer, suction apparatus, endotracheal tube, tracheostomy set, oxygen tank and mechanical respirator.

If coma persists, a detailed program of daily care is essential, both to accelerate recovery and to minimize the complications arising in the unconscious state.

REFERENCES

1. Brain, R.: The physiological basis of consciousness; a critical review, Brain 81:426, 1958.
2. Lindsley, D. G.: Attention, Consciousness, Sleep and Wakefulness, in Field, J. (ed.): *Neurophysiology,* Vol. III, *Handbook of Physiology* (Washington, D. C.: American Physiological Society, 1960), chap. 64.
3. Magoun, H. W.: *The Waking Brain* (Springfield, Ill.: Charles C Thomas, Publisher, 1958).
4. Jefferson, G.: The Reticular Formation and Clinical Neurology, in *Reticular Formation of the Brain* (Boston: Little, Brown & Company, 1958), chap. 36.
5. Walker, A. E.: In *Reticular Formation of the Brain* (Boston: Little, Brown & Company, 1958), p. 743.
6. Engel, G. E., and Romano, J.: Delirium, a syndrome of cerebral insufficiency, J. Chronic Dis. 9:260, 1959.
7. Rosomoff, H. L.: Some effects of hypothermia on the normal and abnormal physiology of the nervous system, Proc. Roy. Soc. Med. 49:358, 1956.
8. Quastel, J. D., and Scholefield, P. G.: Biochemical aspects of cerebral dysfunction, Am. J. Med. 25:420, 1958.
9. Fazekas, J. F.: Pathologic physiology of cerebral dysfunction, Am. J. Med. 25:89, 1958.
10. McDowell, F., and Wolff, H. G.: *Handbook of Neurological Diagnostic Methods* (Baltimore: Williams & Wilkins Company, 1960), p. 179.
11. Adams, R. D.: Coma and Related Disturbances of Consciousness, in Harrison, T. R. *et al.* (eds.): *Principles of Internal Medicine* (New York: McGraw-Hill Book Company, Inc., 1958), chap. 33.
12. Cairns, H.: Disturbances of consciousness with lesions of the brainstem and diencephalon, Brain 75:109, 1952.
13. Dott, N. M.: Brain, movement and time, Brit. M. J. 2:12, 1960.
14. McLaurin, R. L., *et al.:* Metabolic response to craniocerebral trauma, Surg., Gynec. & Obst. 110:282, 1960.
15. Watkins, E. S., Stubbs, J. D., and Lewin, W.: Urea in the management of head injuries, Lancet 1:358, 1961.
16. Austen, F. K., Carmichael, M. W., and Adams, R. D.: Neurologic manifestations of chronic pulmonary insufficiency, New England J. Med. 257:579, 1957.
17. Adams, R. D., and Foley, J. M.: Neurological disorder associated with liver disease, A. Res. Nerv. & Ment. Dis., Proc. 32:198, 1953.
18. Summerskill, W. H. J.: Aguecheek's disease, Lancet 2:288, 1956.
19. Posner, J. G., and Plum, F.: The toxic effect of carbon dioxide and acetazolamide in hepatic encephalopathy, J. Clin. Invest. 39:1246, 1960.

20. Nickerson, J. F., *et al.:* Fatal myxedema with and without coma, Ann. Int. Med. 53:475, 1960.
21. Randall, R. E., Jr., Rossmeisl, E. C., and Bleifer, K. H.: Magnesium depletion in man, Ann. Int. Med. 50:257, 1959.
22. Felts, J. H.: The use of the artificial kidney in poisonings, North Carolina M. J. 21:490, 1960.
23. Hoefnagel, D.: Toxic effects of atropine and homatropine eyedrops in children, New England J. Med. 264:168, 1961.
24. Byers, R. K.: Lead poisoning: review of the literature and report of 45 cases, Pediatrics 23:585, 1959.